IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	09/674,962	Conf. No.	:	7018
Appellant	:	HAUER, Bernhard	Filed	:	Nov. 8, 2000
Examiner	:	WESSENDORF, Teresa	TC/A.U.	:	1639
Docket No.	:	49041	Customer No.	:	26474

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Commissioner for Patents
P.O. Box 1450
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AMENDED BRIEF ON APPEAL

(37 C.F.R. § 41.37)

Honorable Sir:

This Amended Brief on Appeal is submitted in response to the Notification of Non-Compliance of December 21, 2007, which indicated that Appellant's Brief on Appeal filed September 27, 2007 did not contain a copy of the Decision on Appeal of April 28, 2007 in the Related Proceedings Appendix. According to 37 CFR § 41.37(d), "[i]f a brief is filed which does not comply with all the requirements of paragraph (c) of this section, appellant will be notified of the reasons for noncompliance and given a time period within which to file an amended brief. If appellant does not file an amended brief within the set time period, or files an amended brief which does not overcome all the reasons for non-compliance stated in the notification, the appeal will stand dismissed." Appellant respectfully submits that the instant Amended Brief on Appeal overcomes the reasons for non-compliance and is timely filed as the Notification of Non-Compliance failed to set a time period for response. Notwithstanding, Appellant respectfully submits the instant Amended Brief is filed within 1-month of the mailing of the Notification of Non-Compliance.

REAL PARTY IN INTEREST

The real party in interest is BASF Aktiengesellschaft, of Ludwigshafen, Germany, as recorded on November 8, 2000 at Reel/Frame 011830/0340.

RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences currently pending. A Decision on Appeal in the above-identified application was mailed by the USPTO on April 28, 2006 (Appeal No: 2005-2596). A copy of the Decision on Appeal is attached in the Related Proceedings Appendix.

STATUS OF CLAIMS

Claims 5-9 are currently pending and are currently rejected under 35 USC § 103(a). Claims 1-4 are canceled.

STATUS OF AMENDMENTS

The claims have not been amended subsequent to the final rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The invention described by Claim 5 relates to a novel peptide comprising SEQ ID NO: 1 wherein the variables X1 to X6 are defined by the following amino acids:

X1= Asn;

X2= Gln, Glu or Arg;

X3= Gly, Thr or Tyr;

X4= Asn or Arg;

X5= Gly or Lys; and

X6= Cys.

(See Specification page 3, line 9 – page 4, line 17). The invention described by Claim 6 relates to a peptide fragment having SEQ ID NO: 3 (See Specification, page 5, line 25). The invention described by Claim 7 relates to a peptide fragment having SEQ ID NO: 3 (See Specification, page 5, line 27). The invention described by Claim 8 relates to a peptide fragment having SEQ ID NO: 4 (See Specification, page 5, line 29). The invention described by Claim 9 relates to a peptide fragment having SEQ ID NO: 5 (See Specification, page 5, line 31).

Each of SEQ ID NOS: 1-5 relate to novel peptide fragments which serve as protein tags for IMAC, which exhibit increased protein selectivity and simplification of protein purification (Specification page 3, lines 1-7).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 5-9 are obvious under 35 U.S.C. 103(a) in view of Volz et al. (Journal of Chromatography), Guerinot et al. (U.S. Patent No. 5,846,821) and Haymore et al. (EP 409,814).

ARGUMENT

The Rejection of Claims 5-9 under 35 U.S.C. §103(a)

Claims 5-9 stand rejected under 35 U.S.C. § 103 (a) as allegedly unpatentable over Volz et al. (Journal of Chromatography) in view of Guerinot et al. (U.S. Patent No. 5,846,821) and Haymore et al. (EP 409,814). The Office Action of February 27, 2007 alleges that "it would

have been obvious to one having ordinary skill in the art at the time of the invention to pick and choose from the 20 naturally occurring amino acid, the ones that can occupy the x positions in the peptide sequence motif of Volz. Haymore, Guerinot and Volz all disclose that the amino acids at the non-critical or intervening residues between the His and Cys metal binding residues are relatively unimportant in the binding of peptide fragments to metals." (Emphasis added). Appellant respectfully traverses the rejection.

1.) The Combination of the References Fails to Disclose Each and Every Element of the Claimed Invention to Support a *Prima Facie* Case of Obviousness.

Appellant respectfully submits that the combination of the references fails to teach each and every element of the claims to support a prima facie case of obviousness. The Examiner asserts that Volz et al. describes a peptide fragment of formula HXHXXXCXXC (SEQ. ID NO:1) in which Leu is present in the position of the peptide fragment corresponding to X^3, and any of the 20 naturally-occurring amino acid residues in the positions of variables X^1-X^6. The Examiner further asserts the pending claims place Ile where Volz et al. place Leu and that based on teachings of Guerinot et al. and Haymore et al., Leu and Ile can be substituted for each other without losing metal binding properties. However, none of the pending claims recite peptides containing Ile in X^3 position. Notwithstanding, the Examiner asserts, in the Response to Arguments section (Page 4), that "although none of the claims recite Ile, it does not obviate the finding of obviousness that any of the 19 amino acid residues, besides Ile can occupy the X positions, as taught by the references." However, as discussed, *infra*, such statement and random substitution is wholly contrary to the principles of the claimed invention, which is directed to

providing novel peptide fragments that exhibit increased protein selectivity and simplification of protein purification when compared with known fragments. (Specification page 3, lines 1-7).

2.) Conservative Amino Acid Substitutions Cannot Be Applied to All Substitutions

The Examiner asserts Guerinot et al. (U.S. Patent No. 5,846,821) describes that conservative amino acid residues (e.g. Leu and Ile) can be substituted for one another, especially in "non-essential" positions such that it would have been obvious to one having ordinary skill in the art at the time the invention was made "to pick and choose from the 20 naturally occurring amino acid[s], the ones that can occupy the x positions in the peptide sequence motif of Volz." However, Appellant respectfully submits that such positions are essential such that Appellants claimed substitutions in such positions supports the non-obviousness of the instant claims.

Additionally, in arguing the Examiner's general assertion regarding conservative amino acid substitutions, Appellant submits that Guerinot et al. specifically states that, "[a] "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain." (column 14, lines 18-21) (Emphasis added). Accordingly, Guerinot et al. defines families of amino acid residues having similar side chains; wherein the family of "non-polar" side chain amino acids is defined to include alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, and tryptophan. (column 14, lines 21-30) (Emphasis added). Additionally, Guerinot et al. concludes "a predicted nonessential amino acid residue…is preferably replaced with another amino acid residue from the same side chain. (column 14, lines 30-33) (Emphasis added). Consequently, contrary to the Examiner's assertion, there is simply no teaching or suggestion to substitute an amino acid of one side chain

family with an amino acid from another side chain family or to simply pick and choose from among the 20 naturally occurring amino acids for each of positions X^1-X^6. "The fact that a claimed species is or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facia* case of obviousness." *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994). "The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." *Id.*, citing *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). "A disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the invention." *Id.*

Furthermore, while the Board of Patent Appeals & Interferences Decision stated that, "the only difference between the prior art peptide fragment and the [claimed] peptide fragment…is a Ile residue at position X^3 instead of a Leu residue, we agree with the [E]xaminer that it would have been obvious to one of ordinary skill in the art to construct a peptide fragment having the claimed conservative amino acid substitution (i.e., a peptide fragment wherein X^3 is a Leu residue)," (page 5, lines 16-18) and further indicated that Guerinot et al., "merely provides evidence of the correctness of the Examiner's position that these two amino acids are functional equivalents," referring to Ile and Leu (page 6, lines 14-15), Appellant respectfully submits that claims 5-9 were amended subsequent to the Decision such that they do not recite "non-polar" side chain amino acids, such as Ile, for position X^3. Rather, Appellant respectfully submits that claims 5-9 recite that position X^3 comprises one of "uncharged polar" side chain amino acids glycine, threonine, and tyrosine. At least according to Guerinot et al., amino acids in "non-polar" and "uncharged polar" families are <u>not</u> regarded as conservative substitutions. (column

14, lines 18-30).

Accordingly, there is no teaching, suggestion or motivation to undertake a "conservative" amino acid substitution and replace a non-polar amino acid with a polar amino acid. Similarly, the Examiner's assertion that any of 20 naturally occurring amino acids may be substituted for one another is unfounded, is contrary to the teachings of the cited prior art references and is not supported prior Decision of the Board of Patent Appeals & Interferences.

3.) The Prior Art Suggests Non-Obviousness & Teaching Away

The Examiner asserts that Haymore et al. (page 4, lines 10-13) confirms the suggestion by Volz et al. that the intervening amino acids denominated as "X" are not critical to the metal binding activity of the peptide. The Examiner further asserts that Haymore et al. (page 17, lines 14-15) states the intervening residues ("X") are not important. To characterize the teachings of Haymore et al. would be to conclude that at the time of the reference, such intervening amino acid residues were not considered critical to metal binding activity. Hence, applying the Examiner's rationale, it would be not have been obvious for one of ordinary skill in the art at the time of the invention to substitute any of the intervening amino acids denominated as "X". Indeed, absent from Haymore et al. is a suggestion or motivation to perform any of the claimed substitutions on intervening residues whatsoever. Therefore, the reference fails to support the Examiner's obviousness conclusion. In fact, further analysis of Haymore et al., as directed by the Examiner, leads one of ordinary skill in the art to conclude the exact opposite, thatt is, according to Haymore et al., substitution of an intervening amino acid denominated as "X" would result in no change in the metal binding activity of the peptide. Appellant respectfully

submits that the prior art, thus, actually suggests that any attempt to substitute an intervening amino acid denominated by "X" would yield no material effect metal binding properties and would be futile in nature. Accordingly, there is simply no teaching, suggestion or motivation in Haymore et al. to undertake the claimed substitutions. Furthermore, the claimed invention proceeds contrary to the accepted wisdom in the art, which serves as strong evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986)

4.) Absence of Teaching, Suggestion, and Motivation to Combine Prior Art

While Appellant appreciates that "[t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents[,]" the U.S. Supreme Court has made clear that an inquiry into whether there was "…a teaching, suggestion, or motivation to combine known elements [provides] a helpful insight." *KSR Int'l v. Teleflex, Inc.,* 550 U.S. ___ (2007). Such an inquiry helps to uphold the well-settled principle that an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.*

In view of the above, Appellant respectfully submits that the Examiner has attempted to render the instant claims obvious, "merely by demonstrating that each of its elements was, independently, known in the prior art" and by using hindsight reconstruction to use "that which the inventor taught against its teacher." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F2d 1540 (Fed Cir 1983). In this regard, Volz et al. (Journal of Chromatography), Guerinot et al. (U.S. Patent No. 5,846,821), and Haymore et al. (EP 409,814) do not disclose or suggest to one

of ordinary skill in the art a desirability of substituting the claimed intervening amino acid residues in order to positively effect metal binding activity of the peptide. Guerinot et al. is directed to "conservative" amino acid substitutions (column 14, lines 18-30) of isoleucine with leucine (non-polar side chain), which when considered in combination with Volz et al. Guerinot et al. does not teach, suggest or motivate one to substitute non-polar side chain amino acid residues with uncharged polar side chain amino acids, as taught by Appellant. Accordingly, it more appears that the Examiner has used hindsight reconstruction and the Appellant's very own disclosure "as a blueprint to reconstruct the claimed invention from the isolated teachings of the prior art," since the "expressed motivation" to make the combination is lacking from the individual references and does not emanate from that knowledge generally available to the skilled artisan. *Grain Processing Corp. v. AmericanA Maize-Prods. Co.*, 840 F.2d 902 (Fed. Cir. 1988). In this regard, while Haymore et al. may be directed to variant peptides having at least one metal-chelating amino acid sequence, Haymore et al. describes that the modification of intervening amino acid residues ("X") is unimportant (page 3, lines 17-27; and page 4, lines 10-11). Consequently, the skilled artisan would not be motivated to make the claimed substitutions, thereby rendering the instant claims nonobvious. Therefore, the possible sources of motivation to combine references: 1) the nature of the problem to be solved; 2) the teachings of the prior art; or 3) the knowledge of persons of ordinary skill in the art, are not satisfied. *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998).

Beyond the "teaching, suggestion, and motivation" test, the Supreme Court suggested further inquiry regarding: 1) whether the problem is recognized by one of ordinary skill in the art; 2) whether the references applied are obvious to use beyond the primary purpose; 3) whether

it would be obvious to try; and 4) whether "common sense" would make the invention apparent. *KSR Int'l v. Teleflex, Inc.,* 550 U.S. ___ (2007). Applying the above considerations to the instant case, it is, first, readily clear that Appellant has identified the problem of increased protein selectivity and simplification of protein purification (page 3, lines 1-7 of the instant application), which problem was not recognized by one of ordinary skill in the art. Second, the primary purpose of the invention of Guerinot et al. is directed to improvements of metal–regulated transporters and uses therefor (e.g. transgenic plants) and does not describe or suggest obvious uses beyond its primary purpose. Third, none of the prior art or the references cited by the Examiner render it "obvious to try" to combine the prior art to create the claimed invention-especially in view of the fact that the cited art teaches not to try (e.g. Guerinot et al. & Haymore et al.). Lastly, "common sense" does not direct the skilled artisan to fit the teachings of the prior art together like pieces of a puzzle since the teachings of Haymore et al. indicates amino acid substitutions of intervening amino acid residues ("X") are unimportant and the teachings of Guerinot et al. indicates only "conservative" substitutions of the same side chain family are capable of replacement.

Accordingly, it is seen that the explicit and implicit teachings of the prior art references do not disclose, teach or suggest that substitution of the intervening amino acid residue "X" would be a desirable modification to increase the metal binding activity of the peptide. Further, it is not reasonably apparent that such modification emanates from that knowledge generally available to the skilled artisan or "common sense." [T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex, Inc.,* 550 U.S. ___ (2007)

Consequently, for at least the reasons set forth above, Appellant respectfully submits that Volz et al. (Journal of Chromatography) in view of Guerinot et al. (U.S. Patent No. 5,846,821) and Haymore et al. (EP 409,814) fails to disclose or suggest each and every feature of claims 5-9 as required to support a *prima facie* case of obviousness.

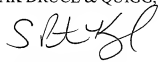
The rejection should be withdrawn.

CONCLUSION

In view of the foregoing, Appellant respectfully asserts that claims 5-9 are nonobvious. Please charge any shortage in fees due in connection with the filing of this paper, including extensions of time, to Deposit Account No. 14-1437

Respectfully submitted,

NOVAK DRUCE & QUIGG, LLP



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Dated: January 11, 2008

CLAIMS APPENDIX

1-4 (Canceled)

5. (previously presented) A peptide comprising SEQ ID NO:1, in which the variables X^1 to X^6 have the following meanings:

X^1= Asn;

X^2= Gln, Glu or Arg;

X^3= Gly, Thr or Tyr;

X^4= Asn or Arg;

X^5= Gly or Lys;

X^6= Cys.

6. (previously presented) A peptide comprising the sequence of SEQ ID NO: 2.

7. (previously presented) A peptide comprising the sequence of SEQ ID NO: 3.

8. (previously presented) A peptide comprising the sequence of SEQ ID NO: 4.

9. (previously presented) A peptide comprising the sequence of SEQ ID NO: 5.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None Pending. A Decision on Appeal in the instant application was mailed on April 28, 2006 (Appeal No: 2005-2596) and is attached.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte BERNHARD HAUER, ROLF D. SCHMID, MARKUS ENZELBERGER, and STEPHAN MINNING

Appeal No. 2005-2596
Application No. 09/674,962

ON BRIEF

ELLIS, SCHEINER and MILLS, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 1-4. According to the examiner, claim 6 has been allowed and claim 5 "would be allowable if rewritten in independent form." Answer, p. 2. Claims 7-18 have been withdrawn from consideration pursuant to 37 CFR § 1.142(b).

As a preliminary matter, we note the appellants' statement on page 3 of the Brief that the claims "have not been argued separately." Accordingly, for purposes of this appeal, we will consider the issues as they apply to claim 1 which is representative of the claims on appeal. Said claim reads as follows:

1. A peptide fragment having the general sequence

His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys (SEQ ID NO:1),

where the variables X^1 to X^6 in the sequence have the following meanings:

X^1 = an amino acid selected from the group consisting of Ala, Val, Phe, Ser, Met, Trp, Tyr, Asn, Asp or Lys and the variables X^2 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^2 = an amino acid selected from the group consisting of Val, Ile, Phe, Pro, Trp, Tyr, Gln, Glu or Arg and the variables X^1, X^3 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^3 = an amino acid selected from the group consisting of Gly, Ile, Thr, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His and the variables X^1, X^2 X^4 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^4 = an amino acid selected from the group consisting of Val, Phe, Pro, Cys, Met, Trp, Asn, Glu, Arg or His and the variables X^1 to X^3, X^5, X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^5 = an amino acid selected from the group consisting of Gly, Ser, Cys, Met, Trp, Asn, Glu, Lys or Arg and the variables X^1 to X^4, X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^6 = an amino acid selected from the group consisting of Phe, Pro, Ser, Cys, Trp, Tyr or Gln and the variables X^1 to X^5 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His and

where at least one of the variables X^1 to X^6 in the sequence is, independently [sic, independent] of one another, Gln or Asn.

The claims stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Volz[1] in view of Guerinot[2] and Haymore.[3]

We have carefully considered the respective positions of both the appellants and the examiner and find ourselves in substantial agreement with that of the examiner. Accordingly, we affirm.

Discussion

As indicated by claim 1, above, the present invention is directed to a peptide fragment comprising a histidine-X-histidine (his or H) and a cysteine-X-X-cysteine (cys or C) motif, wherein "X" represents another amino acid. According to the specification, polypeptides or fusion proteins which contain the peptide fragment of claim 1 "can be purified easily, at low cost" [p. 9, lines 15-17] by bringing said polypeptides in "contact with immobilized metal ions so that an affinity linkage between the [polypeptide] and the metal ions can form [page 10, lines 33-35]."

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). To that end, it is the examiner's responsibility to show that some objective teachings or suggestions in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art

[1] Volz et al. (Volz), "Molecular Characterization of Metal-Binding Polypeptide Domains by Electrospray Ionization Mass Spectrometry and Metal Chelate Affinity Chromotagraphy," Journal of Chromatography A, Vol. 800, pp. 29-37 (1998).
[2] Guerinot et al. (Guerinot), U.S. Patent No. 5,846,821, issued December 8, 1998.
[3] Haymore et al. (Haymore), EPA 409 814, published January 23, 1991.

to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). This the examiner has done.

Volz discloses that peptides containing H-X-H sequences bind with high affinity to nickel (Ni^{2+}) and copper (Cu^{2+}) ions. Volz, p. 29, the abstract. Volz further discloses that C-X-X-C sequences, which are present in zinc finger proteins, bind to Cu^{2+}, Zn^{2+} and Ni^{2+}. Id., p. 29, col. 1. Volz still further discloses that polypeptides which contain an H-X-H-X-X-X-C-X-X-C motif bind to Ni^{2+} and Cu^{2+}. Id., p. 32, col. 2, last complete sentence; Figure 2; p. 37, col. 1. The examiner points out that the peptide fragment disclosed by Volz is identical the peptide fragment set forth in claim 1 except the prior art fragment has a leucine (Leu) residue at position 9 (X^3 of the claimed general sequence), rather than an isoleucine (Ile). Answer, p. 4. To establish that this minor difference in amino acid sequence would have been obvious to one of ordinary skill in the art, the examiner relies on Guerinot's disclosure that Leu and Ile are conservative amino acids. Thus, the examiner argues that "one can replace the other without the loss of peptide activity." Answer, p. 5. The examiner further argues that Haymore discloses that the intervening amino acids between the His residues in metal binding peptides are not important. Id. (relying on Haymore, p. 4, lines 10-13). The examiner concludes that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to replace Leu in the peptide fragment of Volz with a homologous amino acid, Ile, as taught by Geurinot" especially since Haymore discloses that the "intervening residues between the His and Cys metal binding residues are [] unimportant in the binding of peptide fragments to metals." Id.

In response, the appellants argue that there is no motivation to combine the teachings of Volz, Geurinot and Haymore. Brief, p. 4. We disagree.

First, we find that the appellants do not contest the examiner's finding that Leu and Ile are conservative amino acids which can substitute for one another. Answer, p. 5.[4] In other words, Leu and Ile are functional equivalents. We point out that our appellate reviewing court has held on several occasions that "[s]tructural relationships often provide the requisite motivation to modify known compounds to obtain new compounds." In re Mayne, 104 F.3d 1339, 1343, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997) citing In re Deuel, 51 F.3d 1557, 1558, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995); see also, In re Dillon, 919 F.2d 688, 693 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)("structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness"). Thus, given the established structural relationship between Leu and Ile, and the teachings of Volz as to peptide fragment having the sequence His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys, wherein the only difference between the prior art peptide fragment and the peptide fragment of representative claim 1 is a Ile residue at position x^3 instead of a Leu residue, we agree with the examiner that it would have been obvious to one of

[4] We point out that Geurinot (col. 14, lines 18-21), also discloses that "[a] 'conservative amino acid substitution' is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain." Geurinot further discloses that leucine and isoleucine have non-polar side chains. Lines 26-27. Thus, it reasonably follows that leucine and isoleucine are conservative amino acids and are members of the same family (of non-polar amino acids).

ordinary skill in the art to construct a peptide fragment having the claimed conservative amino acid substitution (i.e., a peptide fragment wherein X^3 is a Leu residue).

Second, this is not a case of first impression. The Court has previously agreed with the Board of Patent Appeals and Interferences that Leu and Ile are functional equivalents. In in re Mayne, the facts involved an invention which had a Leu residue at a particular position in a protein; whereas, the prior art protein contained an Ile residue at said position. The Court stated that "Leu is an isomer of Ile—an identical chemical formula with differences only in the chemical bonding of the atoms. The side chains, also known as R-groups, of Leu and Ile have the same number of hydrogen and carbon atoms. Both are nonpolar, hydrophobic amino acids. The structure of Leu and Ile alone suggest their functional equivalency."

In view of the known structural relationship between Leu and Ile, we find that the teachings of Volz alone would have suggested the claimed invention to one of ordinary skill in the art. Guerinot merely provides evidence of the correctness of the examiner's position that these two amino acids are functional equivalents. We further find that the teachings of Haymore are cumulative in that like Volz the patent application discloses that it is the spacing or distance between the two histidine and two cysteine residues which is important and not the amino acid composition itself.

We find the appellants' arguments that (i) Volz does not teach a method of using the H-X-H-X-X-C-X-X-C motif to purify other proteins; and (ii) the claimed amino acid sequences "bind to immobilized metal ions at least 1.5 times more strongly than" that which is taught by Volz, to be misdirected. Brief, p. 5. First, representative claim 1 is directed to a composition and not to a method of use. Second, the claim does not require any specific level of binding to a metal ion. Thus, these arguments do not address a limitation present in the claims.

To the extent that the appellants might have intended to argue that the ability of the claimed protein to bind a metal ion 1.5 times more strongly than the prior art protein (of Volz) is evidence of an unexpected result, we agree with the examiner that, at best, the specification only discloses one clone, M13, which binds at that affinity. Answer p. 7 (relying on page 20, lines 42-44). Thus, this argument is not commensurate in scope with the invention set forth in representative claim 1. Moreover, as pointed out by the examiner, for a showing of unexpected results to be probative evidence of nonobviousness, the appellants must not only establish that there is a difference between the results obtained for the claimed invention and those of the prior art, but they must also demonstrate that the difference obtained is significant and would not have been expected by a person having ordinary skill at the time the invention was made. In re Freeman, 474 F.2d 1318, 1324, 177 USPQ 139, 143 (CCPA 1973); In re D'Ancicco, 439 F.2d 1244, 1248, 169 USPQ 303, 306 (CCPA 1971). This the appellants did not do.

Accordingly, the rejection is affirmed.

Another Issue

Upon return of the application to the corps, the examiner may wish to reconsider whether claims 5 and 6 are patentable over the teachings of the applied prior art. We point out that in the Answer (page 9), the examiner argues that "Volz positively teaches the essential or critical residues for metal ion binding are the His and Cys residues." In this regard, we find that Volz refers to the different metal ion binding regions as "motifs." For example, Volz describes the correspondent peptide as containing a H-X-H-X-X-X-C-X-X-C motif. See, e.g., the abstract. Thus, Volz suggests, and Haymore confirms (p. 4, lines 10-13), that the intervening amino acids denominated as "X" are not critical to the metal binding activity of the peptide. In addition, Haymore states that the intervening residues are not important. Therefore, the examiner should consider whether the teachings of Volz and Haymore would have suggested that any naturally-occuring amino acid could be used in the H-X-H-X-X-X-C-X-X-C motif. This would include the amino acids recited in claims 5 and 6.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Joan Ellis)
Administrative Patent Judge)
)
)
Toni R. Scheiner) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
Demetra J. Mills)
Administrative Patent Judge)

JE/jlb

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